REMARKS

I. Status Summary

Claims 1-27, 46-53, and 60-73 (updated numbering as described in more detail hereinbelow) are pending in the present U.S. patent application. The Official Action dated September 7, 2004 recites that claims 1-27, 46-53, and 61-72 are currently pending. Applicants respectfully submit that claim 60 has not been canceled or withdrawn.

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5231-5236 (hereinafter "Diehl"). Claims 1-4 have also been rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy").

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans"), and further in view of Hedrich (1981) Genetic Monitoring, Volume 1, Chapter 8 (hereinafter "Hedrich"). Claims 1 and 60-72 have also been rejected under this section over the combination of Diehl in view of Bander *et al.* (1989) *Genetical Res* 54:219-219 (hereinafter "Shire").

Claims numbered 69 (second occurrence) through 72 have been renumbered as claims 70-73 in order to correct a numbering error that first appeared in the response to the prior Official Action. In Amendment C, two new claims were numbered as "claim 69". Applicants respectfully submit that the amendments that appear in newly numbered claims 70-73 are solely to correct this numbering error, and are not to be interpreted as a surrender of any subject matter encompassed by the claims as presented in Amendment C.

Claims 60 and 64 have been amended. Support for the amendments can be found throughout the specification as filed, including *inter alia* in the original claims. Additional support for the amendment to claim 60 can be found in the specification as filed at page 6, lines 11-14. Additional support for the amendment to claim 64 can be found at page 6, lines 10-12' page 11, lines 30-32; page 19, lines 11-12; and page 20,

lines 17-21. Accordingly, no new matter has been added as a result of the claim amendments.

New claims 74 and 75 have been added. Support for the new claims can be found throughout the specification as filed, including *inter alia* in the original claims (*e.g.* claims 46 and 47 support new claim 74). Additional support can be found in the specification as filed at page 18, lines 14-19 and in Figure 1 (crossing RI lines to induce heterozygosity), on page 4, line 32, through page 5, line 3 (importance of being able to reproduce genotypes), on page 8, lines 25-27 (regenerating the population of recombinant and genetically diverse individuals), and on page 18, lines 5-8 (definition of "renewable population of genetically diverse individuals" refers to a population that can be faithfully regenerated). Accordingly, no new matter has been added as a result of the new claims.

Reconsideration of the application based on the remarks set forth below is respectfully requested.

II. Interview Summary

On January 13, 2005, a telephone interview was held between applicants' representative Christopher P. Perkins and Examiners Fredman and Sakelaris of the United States Patent and Trademark Office (hereinafter "the Patent Office"). Tentative agreement was reached concerning the overall difference between the claimed subject matter and mapping strategies based on the use of recombinant inbred strains, a difference being that members of RI strains are homozygous at every locus, and the strategy envisioned by applicants involves the use of intentionally non-homozygous individuals. Examiner Fredman suggested that by incorporating the crossing or backcrossing of RI lines into the main claim (*e.g.* by combining the elements of claims 1 and 60), the anticipation rejection would be removed. Applicants' representative Perkins asserted that this should also remove the obviousness rejection because the cited art was based on the generally accepted strategies of employing RI lines (*i.e.* taught that homozygosity was critical), and the instantly claimed subject matter would thus involve heterozygous animals. Although the Patent Office appeared to suggest

that such an amendment might remove one or more of the obviousness rejections, a final agreement was not reached.

Examiner Fredman next asserted that the phrase "renewable population of genetically diverse individuals" reads on any breeding of individuals, including for example the production of human offspring. It was pointed out that this would not result in the production of genomes that are identical (*i.e.* the resultant population would not be genetically renewable), but the Examiner suggested that this element is not clear from the claim language.

Applicants would like to thank Examiners Fredman and Sakelaris for their time and efforts in discussing the instant subject matter during the January 13 telephone interview. Applicants respectfully submit that that the amendments and remarks presented herein are believed to be consistent with their understanding of the Patent Office's positions as presented during the telephone interview.

III. Claim Rejections Under 35 U.S.C. § 102(b)

III.A. The Rejection Over Diehl

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl. The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci (Col2a1, Col1a1, and Col3a1) that modulate a phenotype (facial clefting) in mice. According to the Patent Office, Diehl "performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse" using recombinant inbred (RI) mouse strains provided by M. Nesbitt. Official Action, page 3. The AXB and BXA RI lines are asserted to be crosses between A/J and C57BL6/J strains which were bred by intercrossing RI lines and maintained as a "renewable population of genetically diverse individuals". Diehl is also asserted to disclose the identification of loci using inbred lines using less than about 100 strains, identifying multiple genetic loci that modulate a phenotype, the modulation of a phenotype by a non-genetic factor (drug exposure), and the identification of an interaction among two or more non-genetic factors and a genetic locus.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that the Patent Office is misinterpreting certain terms in the claims. The Patent Office cites various court cases for the proposition that the claims must be given their broadest reasonable interpretation consistent with the specification. Applicants agree. However, applicants respectfully submit that the Patent Office is attempting to interpret the claims in a manner that is inconsistent with the specification. Specifically, the Patent Office has interpreted "renewable" and "genetically diverse" in ways that are not consistent with how these terms are used in the specification.

For example, the Patent Office has apparently interpreted "renewable" to include, for example, human offspring. Applicants respectfully submit, however, that the present specification makes clear that the "renewable population" must be regenerable identical individuals. This difference is clear from the "Background Art" section of the specification, which outlines the shortcomings of mapping using various types of populations. Page 3, lines 26-29, of the present specification, for example, state that mapping F2 populations offer limited interpretation because they are non-regenerative. Page 4, lines 27-29, of the present specification state that after backcrossing or intercrossing an F1 population generated from a Recombinant Inbred Segregation Test, each animal has a unique recombinant genotype, but that the recombinant inbred genotype cannot be reproduced by natural or assisted mating. Additionally, the present specification beginning on page 4, line 32, clearly states: "natural populations encompass individuals that are genetically diverse and each genotype is unique. However, environmental effects cannot be efficiently controlled since the unique genotypes cannot be reproduced by natural or assisted mating" (emphasis added).

Accordingly, applicants respectfully submit that the term "renewable" as used in the specification and the claims refers to the fact that the exact and unique genomes of the population can be regenerated. Human populations are not "renewable" because due to recombination that occurs during meiosis, the genomes of the

population cannot be regenerated by natural or assisted mating. This same recombination occurs in inbred lines, but the recombination event exchanges identical material, resulting in no change to the genome.

Thus, a renewable population is a population the genomes of which can be regenerated to produce individuals that are genetically identical to their predecessors. Applicants respectfully submit that this interpretation is clear from the specification, and is inconsistent with the interpretation the Patent Office is attempting to use. This interpretation is reflected in the definition presented on page 18, lines 5-8: "The phrase 'renewable population of genetically diverse individuals' refers to a population that can be faithfully regenerated and comprises a limited repertoire of possible genotypes, although individuals within the population are genetically diverse". Human populations and F2 populations cannot be faithfully regenerated (except, perhaps, by cloning). Thus, the Patent Office's interpretation of "renewable" is inconsistent with the specification.

Turning now to the Patent Office's interpretation of "genetically diverse", it appears that the Patent Office has defined "genetically diverse" as referring to genomes that are not identical, or alternatively, that contain genetic material that is derived from multiple sources (*e.g.* not from just one non-recombinant inbred strain). However, applicants respectfully submit that this is also inconsistent with the specification. Applicants respectfully direct the Patent Office's attention to the Brief Description of Figure 3, page 9, lines 4-12, of the present specification, which recites the following:

> Figure 3 is a graphical illustration of the power to detect a target gene using a renewable population of genetically diverse individuals (■) or using recombinant inbred populations (▲) having a same number of individuals. In this simulation, the phenotype has a high environmental noise and a fixed background genetic noise representing 13% (arrow) of the total phenotypic variance contributed by a single secondary locus. When a target gene accounts for 13% of the total phenotypic variance, the power to detect the target gene is about five times greater using a renewable population of genetically diverse individuals as compared to a recombinant inbred population.

Applicants respectfully submit that the final sentence of this paragraph clearly indicates that recombinant inbred populations (*e.g.* RI lines) are not populations of genetically diverse individuals (*e.g.* are not populations of heterozygous individuals). However, recombinant inbred populations are recombinant: *i.e.*, they are derived from two or more parents with non-identical genomes.

Thus, the term "recombinant" does not imply that the individuals within a line are "genetically diverse" as that latter term is used in the specification and claims. Under the Patent Office's apparent definition, however, "recombinant" is equivalent to "genetically diverse", and applicants respectfully submit that this definition is inconsistent with the specification.

Summarily, applicants respectfully submit that the Patent Office is interpreting the claim terms in a manner that is inconsistent with the overall teaching of the specification. Applicants respectfully submit that when the claim terms are appropriately construed, it is clear that the claims are patentably distinguishable over the cited references, as discussed in more detail hereinbelow.

Turning now to the Patent Office's characterization of Diehl, applicants respectfully submit that the Patent Office has also misinterpreted the Diehl disclosure. The Patent Office asserts:

> AXB and BXA recombinant inbred (RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then bred by intercrossing recombinant inbred lines and maintained as a colony at the University of Michigan as a renewable population of genetically diverse individuals.

Official Action at page 3, *citing* Diehl at page 5232 (emphasis added).

Applicants respectfully submit that page 5232 of Diehl recites in part the following:

> RI lines derived from crosses between A (A/J) and B (C57BL6/J) strains were supplied by M. Nesbitt. Mice were then bred and maintained in a colony at the University of Michigan.

Diehl at page 5232 (citations omitted and emphasis added). While the difference between "breeding" and "intercrossing" RI lines might seem minor, applicants

respectfully submit that the difference is significant. With respect to the disclosure of Diehl, it is clear that the authors obtained RI lines from M. Nesbitt and propagated them. To be useful, the breeding strategy would have been designed to maintain the RI lines to ensure the continued homozygosity of the individuals. Thus, applicants respectfully submit that the authors did not intercross RI lines as asserted by the Patent Office. Rather, they bred within RI lines in order to maintain the integrity of the RI lines (*i.e.* their homozygosity at every locus), not between lines, which would have destroyed the homozygosity within the lines.

Stated another way, Diehl teaches the maintenance and use of RI inbred lines, the purpose of which would have been defeated if different RI lines were intercrossed as asserted by the Patent Office. RI lines are established by inbreeding, and prior to the disclosure of the instant specification, one of ordinary skill in the art would have believed that the usefulness of the RI lines would have been destroyed if members of one RI line were crossed to members of another RI line. Since the lines received by the authors of Diehl from M. Nesbitt were already established, males and females from within a given line would have been bred to each other to maintain the line. This breeding is not an "intercross". Applicants respectfully submit that "bred" and "intercrossed" are not equivalent terms, and thus the instant assertion is contrary to the disclosure of the cited reference.

Continuing with the instant rejection and upon careful consideration of Diehl, applicants respectfully submit that Diehl also does not disclose each and every element of independent claims 1 and 46. Specifically, Diehl does not disclose a renewable population of genetically diverse individuals that are heterozygous for a detectable polymorphism as recited in claims 1 and 46. Applicants respectfully submit that Diehl discloses standard recombinant inbred strains, which one of ordinary skill in the art recognizes to be strains of mice that are homozygous at every locus. Applicants further respectfully submit that crossing or backcrossing different RI lines destroys the homozygosity that is critical to the use of RI lines in genetic mapping. Thus, applicants respectfully submit that Diehl does not anticipate claim 1 or claim 46.

The Patent Office has attempted to rebut these arguments by asserting that page 5231 of Diehl discloses the creation of a congenic strain by backcrossing the inbred strain A/WySn. According to the Patent Office,

> Diehl's teaching of congenic strains does teach heterozygosity as congenic inbred strains of mice are as genetically like the mice of existing inbred strains as possible in all respects, EXCEPT for alleles at one known locus at which two to four alleles have been deliberately kept segregating (*i.e.* heterozygosity has been forced upon a particular locus).

Official Action at page 5.

Applicants wish to point out, however, that this disclosure does not support a rejection under § 102 because a congenic strain is not heterozygous at any locus. As disclosed in the instant specification, "a congenic line is a recombinant inbred line wherein alternative alleles all reside in a limited chromosomal interval. Recombinant congenic strains are produced by a series of backcrosses to a parent line followed by inbreeding". Specification at page 12, lines 21-24 (citations omitted). Applicants thus respectfully submit that the Patent Office has misinterpreted the nature of congenic strains. Applicants respectfully submit that congenic strains are strains that are identical except at one known locus, but that each member of a congenic pair is still homozygous at this locus.

This difference is best described by example. With reference to the disclosure of Diehl, a congenic strain was developed by backcrossing A/WySn (a susceptible strain; hereinafter "A") to an unnamed strain, which for the purposes of this discussion can be called the R strain (resistant). Thus, an initial cross involved A and R, which produced pups that were genetically 50% A and 50% R. These pups were then backcrossed to R for several generations (typically at least 5, preferably at least 10) to produce pups that genetically had a greater and greater proportion of their genomes derived from R in each subsequent generation. At each breeding stage, however, pups to be bred were selected based on their still being susceptible: *i.e.* they still had the susceptibility locus from A.

At each stage, therefore, the genomes that were chosen for breeding had more and more R, but retained the susceptibility locus from A. After sufficient breeding

steps, the resultant strain would be virtually 100% R with the exception of the susceptibility locus from A. Once this strain is produced, males and females from the strain are intercrossed to produce congenic strains that are characterized by the following: (a) they are homozygous for R everywhere in their genomes except at the susceptibility locus; and (b) they are also homozygous for the susceptibility locus from A. Once homozygosity is established everywhere in the genome for R and at the susceptibility locus for A, then and only then is the strain a congenic strain.

As a result, the Patent Office's assertion that "heterozygosity has been forced upon a particular locus" is inaccurate as to an individual mouse because the individual mouse is homozygous at every locus for either an R allele or an A allele. The "forcing of heterozygosity" refers only to the fact that when compared to individuals of the R line (*i.e.* the inbred line used to create the congenic strain and the other member of the "congenic pair"), the genomes differ at this one locus. Thus, another breeding of the congenic strain to R would segregate alleles at the susceptibility locus. But, breeding a female from the congenic line to a male from the congenic line would not result in segregation at this locus, because the males and females of inbred lines such as congenic lines are genetically identical (*i.e.* homozygous at every locus). This is the hallmark of inbred lines such as recombinant inbred lines, and as congenic strains are recombinant inbred lines, they must be homozygous at every locus. Accordingly, applicants respectfully submit that even the individuals that make up the congenic line of Diehl are not heterozygous for a detectable polymorphism as recited in claims 1 and 46, and thus do not support an anticipation rejection of these claims. As a result, applicants respectfully submit that neither Diehl's disclosure of RI lines nor its disclosure of congenic strains teaches individual mice that are heterozygous at any locus.

Thus, applicants respectfully submit that Diehl does not anticipate claim 1 or claim 46. Claims 2-10, 15, 19-27, and 47-53 all depend directly or indirectly from claim 1 or from claim 46, and thus are also believed to be distinguished from Diehl. Accordingly, applicants respectfully request that the rejection of claims 1-10, 15, 19-27, and 46-53 based on Diehl be withdrawn. Allowance of these claims is also respectfully requested.

III.B. The Rejection Over Bellamy

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy"). According to the Patent Office, Bellamy teaches a method for identifying a genetic locus that modulates a phenotype comprising (a) providing a renewable population of diploid humans that are genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Further, Bellamy is asserted to teach the above method wherein the renewable population comprises a panel of cell lines derived from the genetically diverse individuals.

After considering the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and submit the following.

The Patent Office asserts that the terms "phenotype" and "mapping genomes" relied on by applicants to distinguish these claims are not explicitly defined in the claims or specification. Initially, applicants respectfully submit that there is no requirement for terms that have art-recognized meanings to be explicitly defined when those terms are being used in a way that is consistent with these art-recognized meanings.

For example, applicants respectfully submit that that the term "mapping" as it relates to genetic mapping of genomes, refers to the identification of a locus that modulates a phenotype and the localization of this locus to a chromosome. The Patent Office, on the other hand, offers the following definition from the University of California biotech website: "determination of the relative locations of genetic information on chromosomes". Applicants submit that the proffered definition is consistent with applicants' usage, but does not describe what Bellamy discloses.

The Patent Office asserts that "the placement and size range of band sharing for first degree relatives in the Gaza family for example, meets the limitation of mapping a genome". Applicants respectfully disagree. Bellamy discloses fingerprinting a genome, but fingerprinting is not mapping. Size ranges for band sharing do not implicate any "relative locations" of any genetic information on any

chromosomes. All Bellamy discloses is that certain multilocus probes appear to light up bands of the same size more often in this population than would be expected if the population were outbred. To determine "relative locations", two or more probes would have to be ordered in relation to each other. Applicants respectfully submit that Bellamy does not teach this.

Additionally, applicants respectfully submit that Bellamy does not teach the relative location of any genetic information on any chromosome. The very nature of the probes that were employed prevents these probes from being used in mapping experiments. In Bellamy, the authors used multilocus probes (not the single locus probes that are required for mapping) to generate DNA fingerprints (not mapping information) in order to investigate whether band sharing in an inbred population was higher than that seen in an outbred population. For example, as shown in Figures 2a-2c of Bellamy, each probe resulted in the generation of numerous bands, and as such, is of little or no value in a mapping strategy. Multiple loci are detected by the probes, and Bellamy does not teach the corresponding location of the genetic information encompassed within any one of these bands on any chromosome. Taken in its entirety, then, applicants respectfully submit that the reference does not teach a "determination of the relative locations of genetic information on chromosomes". Thus, Bellamy does not teach a mapping step, and as such does not support an anticipation rejection of claim 1.

Furthermore, the Patent Office asserts that "the phenotype that is modulated is the increased band sharing as evidenced by using four different multi-locus probes". Applicants respectfully submit that increased band sharing is not a phenotype as that term is understood by one of ordinary skill in the art or as it is used in the instant application. According to the specification as filed, "the term 'phenotype' or 'trait' each refers to any observable property of an organism, produced by the interaction of the genotype of the organism and the environment". The proffered definition by the Patent Office also states that a phenotype "is a visible characteristic of an organism".

Applicants respectfully submit that band sharing (a) is not "an observable property of an organism (at best it is an observable property of a population), and (b) does not arise from an interaction of the organism's genome with the environment. As

such, a phenotype is something that is a characteristic of an individual, and does not require reference to the rest of the population. Thus, applicants respectfully submit that band sharing is not a "phenotype" as that term is used in the instant application or is understood by the skilled artisan. Accordingly, applicants respectfully submit that Bellamy does not anticipate claim 1 because the reference does not disclose any phenotype that was mapped.

Moreover, applicants respectfully submit that the Patent Office is incorrect in asserting that increased band sharing is modulated by a genetic locus. Rather, increased band sharing is a passive consequence of the fact that the population in question is an inbred population. Therefore, applicants respectfully submit that the increased band sharing that was observed is wholly independent from the activity of any locus, and instead is based on the artificially low degree of genetic diversity in the inbred population versus an outbred population.

Stated another way, applicants respectfully submit that all Bellamy shows is that inbreeding results in certain chromosomal segments (*i.e.* "bands") becoming "fixed" in an inbred gene pool. Applicants respectfully submit that Bellamy does no more than show that the presence of this phenomenon in the population in question indicates that the population is an inbred population. This phenomenon is not "modulated" by the activity of any gene product.

Claim 1, on the other hand, recites identifying a genetic locus that modulates the phenotype. Applicants respectfully submit that the "phenotype" disclosed in Bellamy (assuming that it is a "phenotype" at all) is not modulated by any genetic locus. Rather, the "phenotype" is simply an observation across a population that arises by breeding within this relatively closed population. Thus, the disclosure of Bellamy cannot be deemed to teach identifying a modifying genetic locus because Bellamy does not involve a situation where any genetic loci are acting to increase or decrease the "phenotype". Accordingly, applicants respectfully submit that Bellamy does not anticipate claim 1 because the reference does not disclose any phenotype that is modulated by any locus.

Summarily, applicants respectfully submit that claim 1 has been patentably distinguished over Bellamy. Claims 2-4 depend from claim 1, and thus are believed

also to have been patentably distinguished over Bellamy. As a result, applicants respectfully request that the rejection of claims 1-4 over Bellamy be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 103

IV.A. Response to the Rejection over Diehl in view of Dindzans and Hedrich

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) J. Immunol 137:2355-2360 (hereinafter "Dindzans"), and further in view of Hedrich (1981) Genetic Monitoring, Chapter 8 in The Mouse in Biomedical Research, volume I (hereinafter "Hedrich"). The bases for these rejections can be found in the Official Action at pages 7-11. Summarily, the Patent Office asserts that:

> it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl et al. so as to have included the diverse population of non-recombinant, parent lines of Dindzans et al. and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents would obviously result in more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best".

Official Action at pages 11-12.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Claims 11-14 and 16-18 all depend indirectly from claim 1, and thus include all of the elements of claim 1. Applicants respectfully submit that none of the cited references disclose or suggest individuals that are heterozygous for a detectable polymorphism as recited in claim 1. This point has been made with reference to the Diehl reference in more detail hereinabove. Applicants respectfully submit that neither Dindzans nor Hedrich cures this deficiency.

With regard to the Dindzans reference, applicants respectfully submit that this disclosure, like Diehl, relates to the use of recombinant inbred strains. As is known in the art, RI strains are homozygous at every locus. This is clearly pointed out in the Dindzans reference itself, which on page 2355 states that "each RI strain consists of a unique assortment of parental genes that are homozygous at every locus", and that "such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control". Thus, Dindzans does not teach or suggest the use of heterozygous mice, and in fact, it teaches against the use of such mice. This is because the homozygosity that is a hallmark of RI lines is that which makes them "useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control".

Turning now to the disclosure of Hedrich, applicants respectfully submit that this reference also teaches the creation of mice that are homozygous at every locus. Applicants respectfully submit that that the citations presented by the Patent Office are from a section of Hedrich entitled "Inbred Strains". As is known in the art, inbred strains are strains that are homozygous at every locus. Thus, the entire Hedrich reference is about generating and maintaining an inbred line, and more particularly is concerned with ensuring that the line maintains its homozygosity at every locus.

This is clearly disclosed on page 170 of Hedrich, which states *inter alia* the following:

- laboratory animal populations are genetically unstable
- strains and substrains deviate in their genotypic structure from the original genetic pattern
- deviant alleles (foreign or new) must be detected, and if possible eliminated, in inbred strains before they are fixed in the homozygous state

Thus, Hedrich teaches the propagation of an inbred strain and ensuring the genetic identity of its members with other members of the strain.

According to Hedrich, this is accomplished by organizing breeding colonies and testing these breeding colonies for the presence of "deviant alleles". On page 171 under the heading "**2. Organization of the Breeding Colonies**", Hedrich states that "the propagation of an inbred strain is divided into three groups: foundation colony

(FC), pedigreed expansion colony (PEC), and production colony (PC)" (emphasis added). Thus, Hedrich discloses breedings designed to maintain an inbred strain.

Furthermore, applicants respectfully submit that all members of the FC, PEC, and PC are members of the same inbred strain. The reference in Hedrich to "selecting among the lines that one which matches the original standards best" is thus not suggestive of introducing heterozygosity, but eliminating it. Applicants respectfully submit that "original standards" refers to the homozygous "genetic profile" that the original inbred strain has (or had). Thus, even the disclosure of "8-10 breeding pairs" in Hedrich does not suggest using 3, 4, or 8 different non-recombinant parent lines to create individuals that are heterozygous for a detectable polymorphism as recited in claim 1 because the entire purpose of the breeding pairs of Hedrich is to maintain a line of mice that are homozygous at every locus by eliminating any deviant alleles (*i.e.* to eliminate polymorphisms). Thus, applicants respectfully submit that the disclosure of Hedrich also teaches against using individuals that are heterozygous for a detectable polymorphism. Accordingly, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich do not teach or suggest all of the elements of the claims, and as such does not support a rejection of claims 11-14 and 16-18 under § 103.

In order to support a *prima facie* case of obviousness, there must also be a suggestion or motivation to combine references to arrive at the claimed invention. Applicants respectfully submit that no such suggestion or motivation can be found. It appears that the Patent Office asserts that the motivation is to gain "the expected benefit that more parents would obviously result in more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making 'it possible to select among the lines that one which matches the original standards best'."

Concerning this last assertion from Hedrich, applicants respectfully submit that the Patent Office has taken one phrase of the reference in isolation, and ignored the context in which the statement appears. As described hereinabove, the "original standards" is the genetic profile of the recombinant inbred strain that Hedrich is trying to maintain. Thus, understood in its proper context, "select[ing] among the lines that

one which matches the original standards best" refers to identifying genetic profiles in the breeding population that are most closely identical to that of the original strain, and breeding those individuals that have that genetic profile to maintain the inbred line.

Applicants further respectfully submit that a mapping method such as the method recited in claim 1 does not "select" individuals qualitatively. Rather, it assesses whether a given phenotype is or is not present. Thus, the Patent Office's proffered motivation, to be able to "select" lines that match the original standards best, is irrelevant in a mapping method, and thus provides no motivation to combine Hedrich with Diehl and/or Dindzans.

Furthermore, applicants respectfully traverse the assertion appearing in the final paragraph of page 11 of the Official Action that Dindzans employed a "diverse population of non-recombinant, parent lines". Applicants stress that Dindzans employed only 2 non-recombinant parent lines: A/J and C57. Similarly, Diehl taught the use of these same two lines, and in a separate experiment taught the use of A/WySn and a resistant inbred line (which was unidentified). Thus, in each case, these authors generated populations that had only one of two possible parental alleles at each locus, and further that every individual was homozygous at every locus. Again, applicants respectfully reiterate that A/J and C57 were the only non-recombinant parent lines taught in Dindzans, and that even with the inclusion by Diehl of A/WySn, which like A/J is simply a substrain of the A strain, none of these references teach breeding together more than two (*e.g.*, 3, 4, or 8) different non-recombinant inbred strains.

The Patent Office further asserts that "Hedrich's teaching of 8-10 breeding pairs makes obvious the use of at least 3, 4, or 8 non-recombinant parent lines of Dindzans". On the contrary, applicants respectfully submit that that this reference does not teach crossing different non-recombinant inbred lines at all. Rather, Hedrich teaches crossing members of the same inbred strain in an attempt to eradicate "deviant alleles", which include spontaneous mutations, contaminating genetic material, etc. Thus, Hedrich cannot be said to motivate one of ordinary skill in the art to employ 3, 4, or 8 non-recombinant inbred lines to create genetically diverse individuals that are heterozygous for a detectable polymorphism because the method

of Hedrich is designed to produce less diverse progeny, not more diverse progeny as contended by the Patent Office.

With regard to the assertion that "more parents would obviously result in more diverse progeny", applicants respectfully submit the following. The Patent Office has not provided any basis for asserting that "more diverse progeny" are desirable as the term "diverse" is being employed in the instant claims. This reference to "more diverse progeny" appears to be derived from the Dindzans citation that states that "the genotype of each RI strain consists of a unique assortment of parental genes that are homozygous at every locus", and that such strains "are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control". However, this interpretation of "diversity" as being related to "unique assortments of parental genes" is not how "diverse" has been employed in the claims.

Applicants respectfully direct the Patent Office's attention to the discussion hereinabove regarding the term "genetically diverse". This term does not refer to a "unique assortments of parental genes". It refers to an individual mouse being heterozygous for one or more detectable polymorphisms (*i.e.* having one or more loci where chromosomal pairs are not identical). Applicants respectfully submit that the claims recite that a genetically diverse individual is an individual that is heterozygous for a detectable polymorphism. Applicants respectfully submit that the Patent Office has not addressed this element of the claims.

This is particularly true with reference to claims 11-14 and 16-18, which recite *inter alia* a method for identifying a genetic locus that modulates a phenotype comprising employing (a) individuals that are heterozygous for a detectable polymorphism that are produced by crossing different RI lines or backcrossing RI lines, wherein the RI lines are derived from at least 3, 4, or 8 different non-recombinant inbred lines; or (b) cell lines derived from said RI lines derived from at least 3, 4, or 8 different non-recombinant inbred lines. As described in more detail hereinabove, each and every one of the cited references teaches the production of mice that are homozygous at every locus, and further that this homozygosity is critical to the usefulness of the methods.

As a result, applicants respectfully submit that each of the cited references teaches against the instantly claimed methods that teach employing genetically diverse (*i.e.* heterozygous) individuals. Consequently, the references contain no suggestion or motivation for the skilled artisan to combine the references as asserted by the Patent Office.

Accordingly, applicants respectfully submit that claims 11-14 and 16-18 have been patentably distinguished from the combination of Diehl, Dindzans, and Hedrich because the combination neither discloses or suggests each and every element of the claims, nor is there any motivation for the skilled artisan to combine the references as suggested by the Patent Office. Applicants respectfully request that the rejection of the claims be withdrawn at this time, and submit that the claims are in condition for allowance.

IV.B. Response to the rejection over Diehl in view of Shire

Claims 1 and 60-73 (updated numbering) have also been rejected under § 103 over Diehl in view of Shire. According to the Patent Office, Shire cures the deficiency of Diehl concerning the crossing or backcrossing of RI lines. More specifically, Shire is asserted to teach reciprocal crosses of the CXBD and CXBE RI strains, C57BL/6ByEss and BALB/cByEss being crossed reciprocally to produce F1 and F2 hybrids, and reciprocal crosses of CXBD/ByEss, CXBE/ByEss, and CXBJ/ByEss. The Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of identifying a genetic locus that modulates a phenotype by providing a renewable population of genetically diverse individuals produced by crossing or backcrossing recombinant inbred lines for the expected benefit of providing a more discriminating test between phenotypic models, as taught by Shire.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Turning to the rejection of claims 1 and 60-73 (updated numbering) generally, applicants respectfully submit that the claims recite *inter alia* methods of identifying

genetic loci by mapping the genomes of genetically diverse individuals. Even assuming *arguendo* that Shire discloses genetically diverse individuals that fall within the meaning of this term as used in the instant application, Shire performs no mapping step, nor does it disclose any locus that has been identified. Thus, at best Shire discloses crossing or backcrossing RI lines, but without the use of the resulting animals in a mapping and identifying method. As such, this reference does not support the deficiencies of Diehl noted above, and thus, this combination of references does not support an obviousness rejection of claims 1 and 60-73 (updated numbering).

To elaborate, the combination does not disclose or suggest mapping and identifying genetic loci that modulate a phenotype. Furthermore, one of ordinary skill in the art would not look to combine Shire's crossing/backcrossing strategy with Diehl to map and identify a locus modulating a phenotype because the method of Diehl relies on homozygosity of the individuals being examined, and Shire's crosses destroy this homozygosity. Thus, the crossing/backcrossing strategy of Shire would destroy the mode of operation of the method of Diehl and render it unsatisfactory for its intended purpose. Thus, applicants respectfully submit that the combination does not support a rejection under 35 U.S.C. § 103. *See* MPEP § 2143.01.

Applicants further respectfully submit that the Patent Office is incorrect in its assertion that a phenotype was modulated by a non-genetic factor in Shire. Applicants respectfully submit that treatment of mice with PMSG and hCG as disclosed results in ovulation and has no effect on any phenotype in mice. This treatment is used extensively in mouse genetics to produce superovulation in female mice, and if it were to have any effect on any phenotype in the offspring, would call into question the analyses of all offspring from the myriad transgenic and knockout experiments that employ the superovulation technique. Thus, particularly with respect to claims 68-72 (updated numbering), which recite the involvement of a non-genetic factor, applicants respectfully submit that neither Shire nor Diehl teaches or suggests this element of the claims.

Furthermore, the phenotype described in Shire is susceptibility to attack by hyaluronidase and pronase of unfertilized eggs. The authors conclude that there is a

locus or loci that are imprinted that affect this susceptibility. There is no disclosure to support the Patent Office's contention that treating females with PMSG and/or hCG modulates (*i.e.*, contributes or alters) this phenotype in any manner. Thus, particularly with regard to claims 68-72 (updated numbering), there is also no disclosure of any phenotype that is modulated by a non-genetic factor. As such, applicants respectfully submit that a *prima facie* case of obviousness has not been presented.

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claims 1 and 60-73 (updated numbering) over Diehl in view of Shire. As such, applicants respectfully request that the rejection of these claims be withdrawn at this time, and the claims allowed. Applicants respectfully solicit a Notice of Allowance to that effect.

V. Discussion of the Amendment to Claim 64

Claim 64 has been amended to recite a method of identifying a genetic locus that modulates a phenotype, the method comprising:

(a) providing a panel of cell lines derived from genetically diverse individuals, wherein the cell lines are animal cell lines;

(b) mapping the genomes of individual cell lines within the panel of cell lines that display the phenotype; and

(c) identifying a genetic locus that modulates the phenotype through the mapping of step (b).

Support for the amendments to claim 64 is discussed hereinabove. Thus, applicants respectfully submit that that claim 64 relates to the mapping of the genomes of cell lines, wherein the cell lines themselves have the phenotype of interest.

Stated another way, unlike mapping efforts that employ cells or cell lines strictly as a source of DNA, the subject matter of claim 64 relates to mapping the genomes of cell lines that express phenotypes of interest. Accordingly, in the method of claim 64 and dependent claims thereof, the cell lines are both the individuals that express the phenotype and the source of DNA to be used in the mapping step. Applicants respectfully submit that while the cell lines are derived from genetically diverse individuals, making the cell lines themselves genetically diverse, it is irrelevant whether

or not the individuals from whom the cell lines are derived express the phenotype. Rather, the subject matter of claim 64 (and dependents thereof) addresses mapping and identifying genetic loci that modulate phenotypes in the cell lines.

Applicants further respectfully submit that these same comments are relevant to the subject matter of claims 2-18 and 47-53 as they relate to panels of cell lines. With regard to these claims as well, applicants respectfully submit that the cell lines are the renewable population of genetically diverse individuals that express the phenotypes of interest. This is illustrated, for example, by the language of claim 2, which recites *inter alia* that the renewable population of genetically diverse individuals comprises (d) a panel of cell lines derived from genetically diverse individuals when taken in view of claim 1 that recites in step (b) that the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype are mapped. As such, applicants respectfully submit that the "individuals that display the phenotype" are the cell lines, because the panel of cell lines is what makes up the "renewable population of genetically diverse individuals" in these embodiments.

Thus, in some embodiments the renewable population comprises a panel of cell lines, and the mapping is performed on members of the renewable population (*i.e.* the panel of cell lines) that display the phenotype of interest. Thus, it is the cell lines and not the individuals from which they are derived that display the phenotype.

As a result, applicants respectfully submit that claims 2-18, 47-53, and 64-73 (updated numbering) have been patentably distinguished over any reference that employs cell lines only as DNA sources (such as, for example, Bellamy). Applicants further respectfully submit that to the best of their knowledge, the present disclosure represents the first efforts to map and identify loci that modulate phenotypes in cell lines derived from animals. Thus, applicants respectfully submit that claims 2-18, 47-53, and 64-73 (updated numbering) are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

VI. Discussion of the New Claims

New claims 74 and 75 have been added. Support for the new claims can be found throughout the specification as filed, including *inter alia* in the original claims

(*e.g.* claims 46 and 47 support new claim 74). Additional support can be found in the specification as filed at page 18, lines 14-19 and in Figure 1 (crossing RI lines to induce heterozygosity), on page 4, line 32, through page 5, line 3 (importance of being able to reproduce genotypes), on page 8, lines 25-27 (regenerating the population of recombinant and genetically diverse individuals), and on page 18, lines 5-8 (definition of "renewable population of genetically diverse individuals" refers to a population that can be faithfully regenerated).

Applicants respectfully submit that the new claims are patentably distinguishable over the combination of Diehl, Bellamy, Dindzans, Hedrich, and/or Shire for the reasons given hereinabove regarding the pending rejections under 35 U.S.C. § 103(a). In particular, applicants respectfully submit that the cited references do not teach or suggest identifying an interaction between a genetic locus and a non-genetic factor using individuals that are heterozygous for a detectable polymorphism produced by crossing or backcrossing different RI lines as recited in claim 74. Additionally, applicants respectfully submit that the cited references do not teach or suggest identifying a genetic locus using a population of genetically diverse individuals for which (a) the genomes are regenerable; and (b) that are heterozygous for a detectable polymorphism as recited in claim 75.

Because the cited references do not disclose or suggest each and every element of these new claims, and further because the cited references do not provide a motivation to the skilled artisan to combine the references to arrive at the claimed invention with a reasonable expectation of success, applicants respectfully submit that new claims 74 and 75 have been patentably distinguished over any combination of Diehl, Bellamy, Dindzans, Hedrich, and Shire. Accordingly, applicants respectfully submit that claims 74 and 75 are also in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

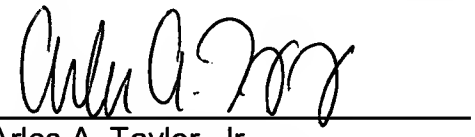
If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 07 March 2005 By: 

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